In utero infection with *Ureaplasma parvum* induces inflammation in the fetal skin

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Objective

Ureaplasma species are the microorganisms most commonly identified (either by culture or qPCR) in association with fetal inflammation and preterm birth. Microbial infection of the amniotic cavity is associated with the **F**etal **I**nflammatory **R**esponse **S**yndrome (FIRS), a systemic inflammatory process defined by the detection of elevated levels of interleukin 6 (IL-6 >11pg/ml) in cord blood. Although there is strong evidence for a link between preterm birth, infection and inflammation, it remains unclear which tissues (maternal, fetal or both) are responsible for the generation of FIRS. The developing fetal skin is constantly exposed, *in toto*, to the amniotic fluid. Using our ovine model of intrauterine infection, we proposed to investigate the ability of the fetal skin to mount a pro-inflammatory response to acute (9 day) and chronic (69 day) infection of the amniotic cavity by *Ureaplasma parvum* svr3.

Methods

Date mated merino ewes were divided into four groups: 1) 5 day intra-amniotic exposure (IAE) of Ups3 (n=5); 2) 9 day IAE of Ups3 (n=5); 3) 69d IAE Ups3 (n=5); and 4) 9d IAE saline (n=4). All ewes were anaesthetised and fetuses delivered by caesarean section at 124d (term=150d). Skin was dissected aseptically from the inner thigh of each fetus and immediately snap frozen in liquid nitrogen. Total RNA was extracted from skin and subjected to a battery of cytokine / chemokine qPCR analyses. To assess immunocyte infiltration in each group, 9μM transverse sections of skin were stained using a standard H&E protocol.

Results

Transverse skin sections demonstrated a marked, progressive thickening and basophilic infiltration of the epidermis at 5, 9 and 69 days post-UPs3 exposure (Fig. 1A). Relative to saline control, qPCR analyses demonstrated large, consistent increases in IL-1β, TNFα and MCP-1 up-regulation at 9 days post-UPs3 exposure and a much lower, more variable response following 69 days exposure (Fig1B).

Conclusions

Cellular infiltration and cytokine / chemokine up-regulation are hallmarks of an inflammatory reaction. *Ureaplasma spp.* are the microorganisms most commonly identified in association with fetal inflammation and preterm birth. These data provide the first controlled experimental evidence demonstrating that the ovine fetal skin possesses the capacity to mount a rigorous pro-inflammatory response following infection of the amniotic cavity by UPs3. On the basis of these observations, we suggest that the fetal skin may make a significant contribution to FIRS and preterm birth following *in utero* infection.